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Morbidity and mortality associated with atherosclerotic peripheral artery disease: A systematic review

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HIGHLIGHTS

- PAD patients have a high risk of all-cause and cardiovascular (CV) mortality.
- Patients with critical limb ischaemia were at highest risk (*versus* ABI < 0.9).
- Fewer patients with critical limb ischaemia received statins (*versus* ABI < 0.9).
- The risk of stroke or MI is at least equivalent to that of coronary artery disease.
- Improved treatments are needed to attenuate CV risk in PAD patients.

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ABSTRACT

Background and aims: It is unclear whether improvements in the detection/treatment of peripheral artery disease (PAD) affect overall survival and morbidity. We undertook a systematic review to describe survival and morbidity in contemporary PAD cohorts.

Methods: Electronic databases were searched for randomised and observational studies reporting mortality/morbidity events between 1 May 2003 and 31 December, 2017 in patients with PAD, diagnosed by intermittent claudication (IC), critical limb ischaemia (CLI), or an ankle brachial index (ABI) < 0.9. Pooled event rates for all-cause and cardiovascular (CV) mortality, non-fatal myocardial infarction (MI), non-fatal stroke, major CV events (MACE; non-fatal MI/stroke, CV death), and major amputation were calculated per 1000 person-years.

Results: 124 eligible studies were identified (570,856 patients; 855,894 person-years of follow-up). Statin use was reported in 67% of the overall cohort and antiplatelet use in 79%. Pooled event rates for all-cause and CV mortality, MI, stroke, MACE, and major amputation were 113, 39, 20, 12, 71, and 70 per 1000 person-years, respectively. Compared with patients with an ABI < 0.9, the presence of CLI was associated with increased rates of all-cause and CV mortality, MI, MACE, and major amputation. Event rates for stroke were similar between patients with an ABI < 0.9 and CLI.

Conclusions: Our data show PAD patients have a high risk of all-cause and CV mortality, and imply the risk of stroke or MI is at least equivalent to the risk in patients with coronary artery disease. Moreover, our data underline the need for improved treatments to attenuate CV risk in PAD patients.

1. Introduction

Atherosclerotic peripheral artery disease (PAD) remains an underdiagnosed and undertreated disease [1,2]. It is estimated that more than 200 million people worldwide are affected [3], which is associated with premature cardiovascular (CV) events and death. The morbidity and mortality associated with PAD are known to be equal to or higher than those associated with coronary heart disease (CHD) [4,5]. This is not surprising, given the common risk factors for atherosclerotic CV disease (CVD) and that patients with PAD often have concomitant

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coronary and cerebrovascular disease [6].

A previous systematic literature review (SLR) from the Ankle Brachial Index (ABI) Collaboration, examining the association between an ABI < 0.9 with mortality and CVD in studies published between 1980 and 2005 [7], reported a 60% excess risk of all-cause mortality and a 96% increase in CV deaths. An update of this SLR is timely because it remains unclear to what extent improvements in PAD diagnosis, the rising number of revascularisation procedures performed, and advances in CV risk modification have an effect on overall survival and morbidity in patients with PAD [8,9]. Furthermore, the clinical spectrum of PAD is wide and includes individuals with symptoms of intermittent claudication (IC) and critical limb ischaemia (CLI), in addition to those diagnosed using the ABI measure of perfusion, who may be asymptomatic. In addition, symptomatic patients with PAD appear to be at higher overall risk of mortality than asymptomatic patients [10,11].

Our objective was to systemically review the current evidence regarding rates of all-cause and CV mortality, myocardial infarction (MI), stroke, major adverse cardiovascular events (MACE; non-fatal MI, non-fatal stroke, CV death), and major amputation in PAD.

2. Materials and methods

2.1. Search strategy

This systematic review was conducted according to the protocol registered with PROSPERO (Registration number CRD42017077983) and in accordance with PRISMA and MOOSE guidelines [12,13]. The online databases MEDLINE, Embase, Cumulated Index to Nursing and Allied Health Literature (CINAHL), and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for medical subject heading (MeSH) and keywords related to PAD, IC, CLI, mortality, MI, stroke, and major amputation (Supplementary Data 1).

These searches were supplemented by examining reference lists of included studies, reviews, and meta-analyses [14,15]. No language restrictions were applied.

Inclusion criteria were as follows: (1) randomised controlled trial (RCTs) and observational studies; (2) reporting mortality or morbidity events recorded between 1 May, 2003 and 31 December, 2017 among patients with PAD, defined as the presence of IC, CLI, or an ABI < 0.9; (3) with ≥200 study participants with PAD; (4) reporting exclusively on individuals aged ≥40. Studies with cohorts including patients with CVD in other vascular beds (e.g., coronary artery disease) were included only if outcomes in patients with PAD were reported separately or if ≥ 80% of the overall cohort had PAD.

2.2. Data extraction and quality assessment

Two reviewers independently screened all titles and abstracts to identify articles suitable for full-text review. These reviewers then independently screened full-text articles, with differences resolved by consensus, and extracted the following data from eligible studies (where available): study details (study name, design, country/countries, number of PAD patients, method of PAD diagnosis, intervention, study period); patient characteristics (age, gender, prevalent obesity, hyperlipidaemia, hypertension, diabetes, smoking history); medication use (statin, other lipid-lowering therapy, antiplatelet, anticoagulation, β-blocker, angiotensin-convertase-inhibitor [ACEi]/angiotensin receptor blockade [ARB]); and outcomes (all-cause mortality, CV mortality, stroke, MI, MACE, and major amputation). For each outcome, the total number of events and mean follow-up duration were extracted, to allow for the calculation of event rates per 1000 person-years.

Following data extraction, two reviewers independently assessed the quality of studies using two separate tools. RCTs were assessed using the Cochrane Risk of Bias Tool. This tool assesses bias as a judgement (high, low, or unclear) for individual study elements from five domains (selection, performance, attrition, reporting, and other) [16]. Observational studies were assessed using the Risk of Bias for Non-Randomised Studies-Interventions (ROBINS-I) tool [17]. This tool assesses bias across seven domains: (1) bias due to confounding, (2) bias in selection of participants, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes and (7) bias in selection of the reported result, and defines overall risk of bias as low, moderate, serious, or critical. Sensitivity analyses excluding studies with unknown, serious, or critical risk of bias for the primary and secondary outcomes were planned.

2.3. Statistical analyses

Where available, summary characteristics of included patients were presented as mean values weighted by study size. The primary outcomes were event rates for all-cause and CV mortality reported per 1000 person-years. Secondary outcomes were event rates for MI, stroke, MACE, and major amputation. Where not directly reported, event rates were calculated by dividing the absolute number of events by the total person-years of follow-up. Pooled event rates were weighted by study size (number of participants with PAD).

Associations between method of PAD diagnosis and outcomes (primary and secondary) were assessed using random-effects analyses (heterogeneity was high, as measured by the I^2 statistic) [18]. Specifically, cohorts including (1) patients with an ABI < 0.9, IC, or CLI (mixed cohort) and (2) patients with a PAD diagnosis based only on CLI (CLI cohort) were compared to patients with a PAD diagnosis based only on an ABI < 0.9 (ABI < 0.9 cohort). These analyses were performed using SPSS Statistics version 25 (IBM) and STATA statistical software version 12 (StataCorp).

3. Results

3.1. Study characteristics

Of 11,520 potentially relevant publications, 807 were identified for full-text review and 124 were included in the final analysis (Fig. 1). The

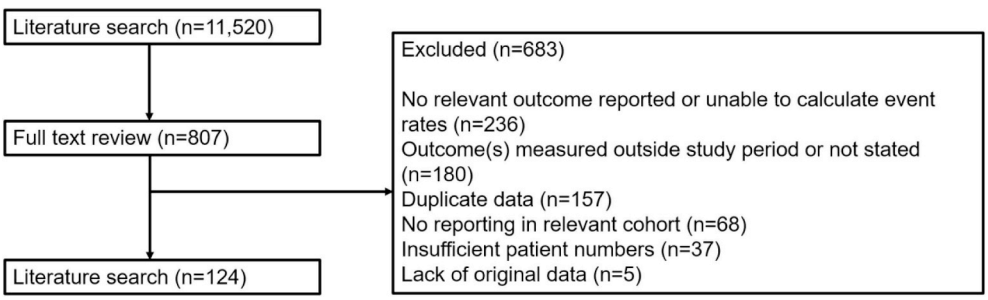

Fig. 1. Study selection.

Table 1
Patient characteristics by method of PAD diagnosis.

	ABI < 0.9 (n = 2708)	CLI (n = 370,754)	Mixed (n = 197,394)	Overall (n = 570,856)
Age, years, mean (SD)	68 (11)	69 (13)	69 (10)	69 (13)
Men, %	50	58	63	60
BMI, kg/m^2 (SD)	28 (5)	25 (6)	28 (5)	27 (5)
Hyperlipidaemia, %	48	42	52	44
Hypertension, %	75	77	77	77
Diabetes, %	42	55	40	50
Smoking history, %	74	44	71	47
Current smoker, %	50	12	27	27
Statin, %	76	55	68	67
Antiplatelet, %	80	82	79	79
Beta blocker, %	48	44	54	53
ACEi/ARB, %	65	52	56	55
Anticoagulation, %	19	17	10	13
CKD[a], %	36[b]	26	18	22

ABI, ankle brachial index; ACEi, angiotensin convertase enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CLI, critical limb ischaemia; SD, standard deviation. Summary statistics are weighted by study size.
[a] Additional data on renal disease are available in Supplementary Data 3.

main reasons for excluding studies were: they did not report any of the primary or secondary outcomes or did not permit calculation of event rates (n = 236 [35%]), outcomes were recorded outside the study period (n = 180 [26%]), or they reported duplicate data (n = 157 [23%]). The majority of included studies were based on cohort studies or registry data (n = 78 [63%] and 27 [22%], respectively); 15% (n = 19) were RCTs (Supplementary Data 2). Included studies reported on event rates in 570,856 patients with 855,894 person-years of follow-up; 107 studies reported all-cause mortality, 23 reported CV mortality, 17 reported stroke events, 21 reported MI events, and 81 reported major amputation events (Supplementary Data 3).

Characteristics of included patients are summarised by method of PAD diagnosis in Table 1. Patient characteristics in individual studies are presented in Supplementary Data 4. Compared with patients with an ABI < 0.9, those with CLI were more likely to be male and diabetic, and less likely to smoke. While prevalence of hyperlipidaemia was similar for patients with ABI < 0.9 and those with CLI (48% and 42%, respectively), statin use was higher in patients with an ABI < 0.9 (76% *versus* 55%, respectively). In the overall PAD cohort, 67% of patients were receiving statins, 55% receiving ACEi/ARB, and 79% receiving antiplatelet medication.

3.2. Main outcomes

Event rates are summarised by method of diagnosis in Table 2. In the overall cohort, event rates for all-cause and CV mortality were 113 and 39 per 1000 person-years, respectively. Compared with patients with an ABI < 0.9, the presence of CLI was associated with an increased event rate for all outcomes studied except stroke (Table 2, Fig. 2). The risk of all-cause mortality was more than two-fold higher among patients with CLI (183 vs 81 events/1000 person-years; Relative risk [RR], 2.26, 95% confidence interval [CI], 1.77–2.89). The risk of MI was also more than two-fold higher among patients with CLI (42 *vs* 16 events/1000 person-years; RR, 2.63, 95% CI, 1.49–4.64), and the risk of major amputation almost four-fold higher (100 *vs* 26 events/1000 person-years; RR, 3.85, 95% CI, 2.52–5.87). The risk of CV mortality and MACE were approximately one and a half-fold higher (74 *vs* 52 events/1000 person-years; RR, 1.42, 95% CI, 1.01–2.01 and 95 vs 55 events/1000 person-years; RR, 1.73, 95% CI, 1.25–2.38).

In exploratory analyses, we compared event rates from studies that commenced before 2008 with those from studies that commenced after 2008. In the overall cohort, event rates for all-cause mortality were similar between the two groups, 111 *vs* 108 per 1000 person-years. Event rates for CV mortality were higher in studies that started before 2008 than in those that started after 2008, 46 *vs* 36 per 1000 person-years, respectively (Supplementary Data 4a). When comparing event rates from studies with longer or shorter observation periods (in comparison to the mean observation period of 1.3 years), event rates for all-cause mortality were higher in studies with a shorter observation period compared with those in studies with a longer observation period (123 versus 82 per 1000 person-years, respectively) (Supplementary Data 4b). We also compared event rates from studies with a median year of observation during the first half of our inclusion period (i.e. 2003–2010) with event rates from studies with a median year of observation during the second half of our inclusion period (i.e. 2011–2017) (Supplementary Data 5.1–5.4). We observed no apparent change in the rates of major amputations; the pooled event rate (70 per 1000 person-years) was the same for studies with a median study year in the first and second halves of our inclusion period. We observed a trend towards decreasing event rates for all-cause mortality (119 vs 108 per 1000 person-years), CV mortality (46 vs 36 per 1000 person-years), and MACE (83 vs 67 per 1000 person-years) in the second half of our

Table 2
Pooled event rates per 1000 person-years by method of PAD diagnosis.

Event rates (range) per 1000 person-years[a]	ABI < 0.9 (n = 2708)	CLI (n = 370,754)	Mixed (n = 197,394)	Overall (n = 570,856)
All-cause mortality	81 (39–173)	183 (25–468)	86 (14–185)	113 (14–468)
CV mortality	52	74 (16–126)	35 (10–75)	39 (10–126)
Stroke	11	9	12 (7–50)	12 (7–50)
MI	16	42 (8–51)	19 (4–65)	20 (4–65)
MACE	55	95 (27–170)	70 (36-230	71 (27–230)
Major amputation	26 (2–103)	100 (10–232)	37 (2–140)	70 (2–232)

ABI, ankle brachial index; CLI, critical limb ischaemia; CV, cardiovascular; MACE, major adverse cardiovascular events. MI, myocardial infarction. Event rates are weighted by study size. Where no range is presented, data derive from a single study.
[a] Of the included studies, 107 reported all-cause mortality, 23 reported CV mortality, 17 reported stroke events, 21 reported MI events, and 81 reported major amputation event.

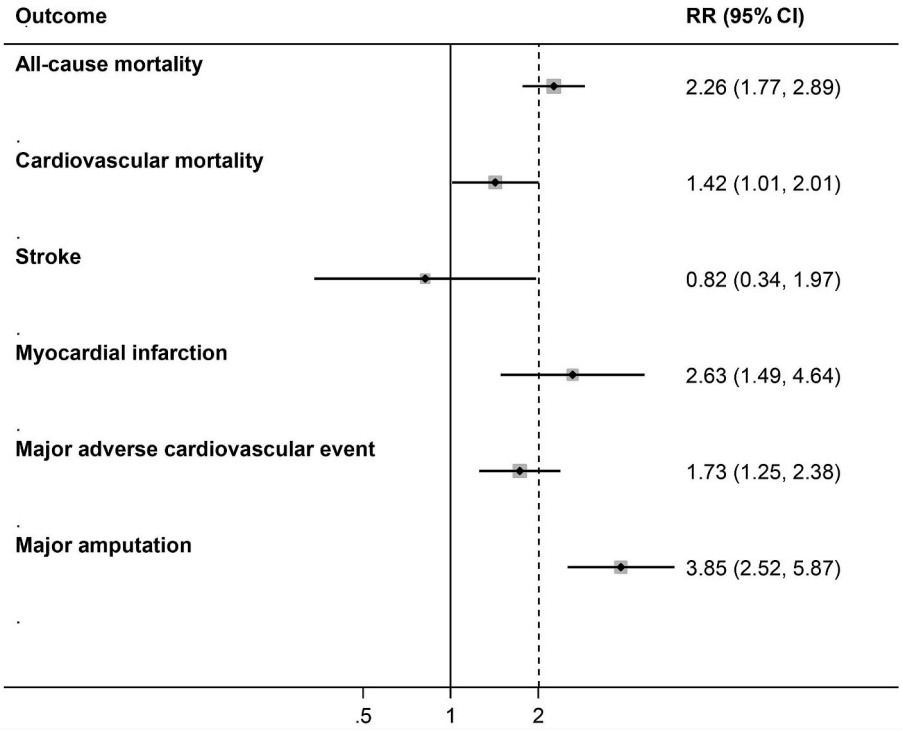

Fig. 2. Association of critical limb ischaemia with outcomes (using patients with ABI < 0.9 as the reference group).
Patients with ABI < 0.9 used as the reference category; ABI ankle brachial index; CLI, critical limb ischaemia; RR, relative risk.

inclusion period. There were insufficient numbers of studies reporting on event rates for stroke and MI to permit meaningful comparisons over time.

Among studies reporting exclusively on patients with CLI, we observed a large variation in event rates for all outcomes, including all-cause mortality, which ranged from 25 to 468 events per 1000 person-years (Table 2). To assess whether this variation was related to study design, patient characteristics and event rates for studies reporting only on patients with CLI were summarised by study design (Table 3). Patients enrolled in RCTs were of a similar age to those enrolled in observational studies. Pooled event rates for all-cause mortality, CV mortality, MI, and MACE were lower in RCTs (88 vs 184, 16 vs 80, 11 vs 47, and 27 vs 123 per 1000 person-years, respectively). Conversely, the pooled event rate for major amputation was higher in RCTs (142 vs 99 per 1000 person-years), which may relate to a higher prevalence of diabetes which was observed in the RCTs.

3.3. Risk of bias

The overall risk of bias for RCTs, measured using the Cochrane Risk of Bias Tool, was low in 17 studies and unclear in 2 studies (Supplementary Data 6). In sensitivity analyses excluding RCTs judged to be of unclear bias, event rates were similar to those observed in the main analyses. The overall risk of bias in observational studies, as assessed using the Robins-I tool, was moderate for all studies (Supplementary Data 7). Our analyses did not assess the effect of any intervention(s) on outcome measures, therefore no study was considered to have deviated from an intended intervention.

Table 3
Critical limb ischaemia patient characteristics and pooled event rates per 1000 person-years by study design.

	RCT (n = 1602)	Observational (n = 369,152)
Patient characteristics		
Age, years, mean (SD)	69 (8)	69 (13)
Men, %	70	58
BMI, kg/m^2 (SD)	28 (5)	24 (5)
Hyperlipidaemia, %	66	42
Hypertension, %	82	77
Diabetes, %	70	56
Smoking history, %	39	44
Current smoker, %	NA	12
Statin, %	58	55
Antiplatelet, %	75	82
Beta blocker, %	46	44
ACEi/ARB, %	60	51
Anticoagulation, %	32	15
Event rates (range) per 1000 person-years		
All-cause mortality	88	184
CV mortality	16	80
Stroke	9	NA
MI	11	47
MACE	27	123
Major amputation	142	99

ACEi, angiotensin convertase enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; NA, not available; RCT, randomised controlled trial; SD, standard deviation.
Summary statistics are weighted by study size. Where no range is presented, data derive from a single study.

4. Discussion

Our systematic review of both RCTs and observational studies shows that PAD carries at least a comparable risk of all-cause and CV mortality events to disease in other vascular beds, as reported in other observational studies. The overall rate of all-cause mortality we observed (113/1000 person-years) exceeds that reported in patients with coronary artery disease in the Cardiovascular Health Study (71/1000 person-years) [19], the Reduction of Atherothrombosis for Continued Health (REACH) registry (26/1000 person-years) [20], and the Renfrew and Paisley cohort (47–51/1000 person-years) [21]. Furthermore, the overall rate of CV mortality we observed (39/1000 person-years) is comparable with the Antithrombotic Trialists' Collaboration meta-

analysis of RCTs enrolling participants with previous MI or stroke (40/1000 person-years) [22].

Our findings extend those of a previous systematic review investigating the association of low ABI with mortality and CVD [7], by reporting event rates stratified by method of PAD diagnosis. In the previous review, which included 11 studies reporting on 44,590 participants, an ABI < 0.9 was associated with an increased risk of all-cause and CV mortality compared with an ABI ≥0.9 (RR, 1.60, 95% CI, 1.32–1.95 and 1.96, 1.46–2.64, respectively). In our study, compared with an ABI < 0.9, the presence of CLI was associated with an increased risk of all-cause and CV mortality (RR, 2.26, 95% CI, 1.77–2.89 and 1.42, 1.01–2.01, respectively), MI (RR, 2.63, 95% CI, 1.49–4.64), MACE (RR, 1.73, 95% CI, 1.25–2.38) and major amputations (RR, 3.85, 95% CI, 2.52–5.87). The event rates for stroke were similar in patients with an ABI < 0.9 or CLI.

The overall event rates in our study also imply that the risk of stroke and MI in a PAD population is at least equivalent to the risk of these events in patients with coronary artery disease (CAD). In the REACH registry [20], event rates for stroke and MI among patients with CAD were 12 and 13 per 1000 person-years, respectively, compared with 12 and 20 per 1000 person-years, respectively, in our study. In the COMPASS study of patients with stable atherosclerotic CVD randomised to rivaroxaban, rivaroxaban + aspirin, or aspirin alone, event rates for the primary outcome of CV death, stroke or MI were higher in the PAD subgroup as compared with the CAD subgroup [23]. The CV event rates reported in our PAD cohort have important implications for preventive therapy, which previous studies have reported to be inadequate [24–26]. The 2011 Practice Guidelines from the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) support the use of an antiplatelet to reduce the risk of CV events among patients with IC, CLI, prior revascularisation or amputation for lower limb ischaemia (Class 1A recommendation) [27].

In our cohort, antiplatelet therapy was reported in 82% of patients with CLI, comparable with that reported among patients with CAD in REACH (86%) [20]. It is less well established whether antiplatelet therapy is indicated in asymptomatic individuals with an ABI ≤0.9 (Class 2C recommendation). The Aspirin for Asymptomatic Atherosclerosis (AAA) trial enrolled 3350 individuals free of clinical CVD with a low ABI (≤0.95) and found no significant reduction in vascular events among patients treated with aspirin 100 mg compared with placebo [28]. Consistent with results from the AAA trial, the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial found no evidence to support the use of aspirin for primary prevention among patients with diabetes and an ABI < 0.99 [29]. Two meta-analyses examining the role of antiplatelet agents among asymptomatic patients with PAD provide conflicting results; Berger et al. reported no benefit of antiplatelets in reducing all-cause and CV mortality [28], whereas the Antiplatelet Trialists' Collaboration analyses support the use of antiplatelet agents (including dipyridamole and ticlopidine) in all patients with atherosclerotic vascular disease [30]. Our findings suggest that antiplatelet therapy among individuals with an ABI < 0.9 may be increasing, with the proportion of patients receiving any antiplatelet therapy in our cohort (2003–2017, 80%) greater than that reported in the National Health and Nutrition Examination Study (1999–2004, 49%).

Analyses of the REACH registry found treatment with ≥2 preventive therapies (including aspirin, statin and/or ACEi/ARB) to be associated with a 65% reduced risk of all-cause mortality among individuals with PAD, as identified by an ABI ≤0.9, but with no prior history of CVD [26]. In our PAD cohort, 79%, 67% and 55% of patients were receiving an antiplatelet, statin and ACEi/ARB, respectively, suggesting there may be opportunity to further reduce CV events through more effective use of preventive treatments. Also of note, fewer patients with CLI in our analyses received statin therapy compared with those with an ABI < 0.9. Given that event rates for CV death, MI and MACE were highest in patients with CLI, this is a potential cause for concern and suggests these patients should be prioritised for CV risk modification.

Until recently, there was insufficient evidence to confirm the role of low-density lipoprotein cholesterol (LDL-C) in the pathogenesis of PAD; indeed several studies showed no significant association between LDL-C levels and incident PAD [3,31]. More recently, in the Scottish Heart Health Extended Cohort (SHHEC) of 15,000 individuals observed for 20 years, LDL-C was identified as an independent risk factor for PAD [32]. Irrespective of its role in the pathogenesis of PAD, a wealth of evidence from observational and randomised studies supports the benefits of LDL-C lowering in a PAD population. In analyses of a REACH subgroup with IC and an ABI < 0.9, statin use was associated with a significant reduction in MACE (HR 0.85, 95% CI, 0.75–0.96) as compared with no statin therapy [33]. Moreover, in patients with PAD, statin therapy was shown to reduce the risk of major adverse limb events (including deterioration of symptoms, peripheral revascularisation, and amputation) by 18% [33]. These findings are supported by RCT evidence from the Heart Protection Study; in a pre-specified subgroup analysis, treatment with simvastatin reduced the risk of a first major vascular event by 22% among patients with symptomatic PAD, compared with placebo [34]. Further beneficial effects of statin therapy have been observed in populations with atherosclerotic CVD including reducing the development or progression of claudication [35], and preventing restenosis following endovascular or open bypass revascularisation [36,37].

Both the intensity of lipid-lowering therapy and LDL-C levels achieved in patients with PAD appear to be determinants of outcome. The randomised Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial included a subgroup of 3642 patients with PAD. In this subgroup, when added to optimised statin therapy, evolocumab significantly reduced the risk of MACE (defined as death, MI, stroke, hospitalisation, or coronary revascularisation) or major adverse limb events (MALE, defined as acute limb ischaemia, major amputation, or urgent peripheral revascularisation) (HR 0.79, 95% CI, 0.66–0.94) [38]. In addition, evolocumab significantly reduced LDL-C levels by 59% compared with placebo, with these reductions maintained over time and a linear relationship observed between lower LDL-C and lower risk of MALE that extended to LDL-C levels below 10 mg/dL. Among patients treated with placebo, those with PAD had a significantly increased risk of death, MI, stroke, hospitalisation, or coronary revascularisation compared with patients without PAD (HR 1.57, 95% CI, 1.36–1.80). In observational studies involving patients with PAD, increasing the intensity of statin therapy has been shown to result in lower rates of all-cause and cardiovascular mortality [39], in addition to reducing rates of lower limb amputation [40].

The event rates for all-cause mortality, CV mortality and MACE observed in our PAD cohort were lower in RCTs than in observational studies. This finding may relate to more optimal management of CV risk in a RCT setting. Conversely, the event rates for major amputation were highest in RCTs. However, patients enrolled in RCTs had a higher prevalence of diabetes, which may explain this finding. Specifically, the broad overlap of CLI and diabetic foot may confound the appropriate classification of PAD [41], with patients with the far higher risk of limb loss associated with diabetic foot, and patients with atherosclerotic CLI being grouped together.

Of note, the event rates for CV mortality observed in our overall cohort were higher in studies that commenced before 2008 compared with the event rates in the studies that commenced after 2008. This suggests that the publication of the 2005 and 2007 guideline recommendations on the management of patients with PAD [42,43] may have helped to improve CV outcomes. Further research to investigate a possible causal relationship between changes in guideline recommendations and improved outcomes in patients with PAD would be of interest.

As with any systematic review, our limitations in part reflect those of the included studies. Data on the outcomes of interest were

inconsistently reported and, in many studies, outcomes were reported in mixed cohorts of patients with IC, CLI, or an ABI < 0.9. Of note, no study reported on IC alone. As such, we were only able to categorise a small number of patients by the method of PAD diagnosis for comparison of event rates. Furthermore, the data set only included patients with an ABI < 0.9, which limited the assessment of risk in individual ABI cohorts; for example, for patients with an ABI > 0.9–1.3 or > 1.3. In addition, the lack of individual patient data precluded analyses adjusted for baseline characteristics, which may have influenced event rates; thus our findings may be subject to residual confounding. Also, the inclusion of observational studies in our analyses may have introduced selection biases.

With data on over half a million patients from 124 studies, our study provides substantially more information on event rates in PAD than previous systematic reviews. Event rates varied widely between studies, reflecting the heterogeneous nature of PAD and the broad spectrum of disease enrolled in the included studies. The variability in event rates may also be partly a result of global variation in prevalence, phenotype and outcomes of patients with PAD. In future studies, it would be of interest to examine the effect of geographical and socio-economic factors on event rates in these patients. Event rates for all-cause and CV mortality in our cohort were comparable to those observed in contemporary cohorts with CAD, highlighting the need for effective treatments to attenuate the risk of CV events. Patients with CLI were at the highest overall risk for all outcomes measured with the exception of stroke, yet fewer patients in this group received statin therapy than patients with an ABI < 0.9. This observation suggests an opportunity to prevent more CV and limb events with lipid lowering therapy.

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Author contributions

Conception and design, interpretation of the data, critical revision of the manuscript, and approval of the final version to be published (GA, JB, IB, PG, UH).

Declaration of competing interest

GA and IB have no conflicts of interest to declare. JB has received consulting fees from Amgen, Sanofi, Rexgenero, Astra Zeneca, and Bayer. UH has received consulting fees from Amgen, Sanofi, Bayer, and Daiichi Sankyo. PG is an employee of Amgen (Europe) GmbH and holds stock options in Amgen Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.09.012.

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